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SELECTIVE ANTAGONISM OF THE RATE-DECREASING EFFECT OF d-AMPHETAMINE BY CHLORPROMAZINE IN A REPEATED-ACQUISITION TASK

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Pigeons acquired a different four-response chain each session by responding sequentially on three keys in the presence of four colors. The response chain was maintained by food presentation under a fixed-ratio schedule. When *d*-amphetamine was administered alone, the overall response rate decreased and the percent errors increased with increasing doses. When a small dose of chlorpromazine, which was ineffective when given alone, was administered in combination with *d*-amphetamine, the rate-decreasing effect was antagonized. The antagonism was selective, however, in that the error-increasing effect of *d*-amphetamine was augmented by chlorpromazine. The nature of the joint effect of the two drugs thus depended on the behavioral measure: rate vs. accuracy.

Key words: repeated acquisition, response chains, fixed-ratio schedule, drug antagonism, *d*-amphetamine, chlorpromazine, key peck, pigeons

The antagonistic relationship between chlorpromazine and amphetamine, in regard to behavioral effects, is a well-documented drug interaction. One would expect this type of relationship on the basis of biochemical data: amphetamine releases norepinephrine and dopamine from nerve terminals containing these catecholamines, whereas chlorpromazine blocks catecholamine receptors (Iversen & Iversen, 1975). With reference to operant behavior, it has been shown, for example, that chlorpromazine can antagonize the rate-increasing effect of amphetamines on Sidman avoidance responding in rats (Brown, 1966; Ray & Bivens, 1968; Teitelbaum & Derks, 1958).

Chlorpromazine has also been shown to antagonize the rate-decreasing effect of *d*-amphetamine on responding maintained by food presentation under small fixed-ratio (FR) schedules in rats (Brown, 1963) and pigeons (Davis, 1965). For example, in the Davis study, responding under an FR 30 schedule served as the baseline. When a large dose of *d*-amphetamine (e.g., 8 mg/kg) was administered before the session, responding was abolished. Responding was restored, however, when a small dose of chlorpromazine (3 mg/kg) was administered during the session. Chlorpromazine also antagonized the rate-decreasing effect of *d*-amphetamine when both drugs were administered simultaneously before the session.

In the Davis (1965) study, a single response key was used. The present research focused on the question of whether similar results would be obtained with more complex operant behavior. A repeated-acquisition baseline was established in which pigeons acquired a different four-response chain each session by responding sequentially on three keys in the presence of four colors; the response chain was maintained by food presentation under an FR 5 schedule. In previous research using this baseline (e.g., Thompson, 1973, 1978; Thompson & Moerschbaecher, 1980), it was found that *d*-amphetamine decreased the overall rate of responding and increased the percent errors with increasing doses. The present research examined the possibility that these effects of *d*-amphetamine could be blocked by chlorpromazine.

METHOD

Subjects

Two adult male White Carneaux pigeons were maintained at approximately 80% of their free-feeding body weights by food presented during the sessions and by postsession

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supplemental feeding. The 80% values were 514 g and 478 g for Pigeon 4039 and Pigeon 3129 respectively. Water and grit were always available in the home cages. Each subject had an extensive history of repeated acquisition of four-response chains under an FR 5 schedule.

Apparatus

The experimental space was a standard three-key pigeon chamber (BRS/LVE model SEC-002). Each translucent response key required a minimum force of .18 N for activation. Each key could be transilluminated by three Sylvania 24ESB indicator lamps, one with a red plastic end cap, one with a green cap, and the third with no cap. To provide a fourth color, "yellow" (actually yellow-orange) was produced by the red and green lights being on simultaneously. The control equipment consisted of timers, steppers, and associated relay circuitry; recording was by counters, running-time meters, and an event recorder. White noise was continuously present in the chamber to mask extraneous sounds.

Procedure

Repeated-acquisition baseline. All three response keys were illuminated at the same time by one of four colors, either yellow, green, red, or white. The pigeon's task was to acquire a four-response chain by pecking the correct key in the presence of each color, e.g., keys yellow—Left correct; keys green—Right correct; keys red—Center correct; keys white—Right correct; reinforcement. The same chain (in this case, Left-Right-Center-Right or LRCR) was repeated throughout a given session. The four-response chain was maintained by food presentation under an FR 5 schedule; i.e., every fifth completion of the chain was followed by 3-sec access to mixed grain. Presentation of the grain magazine was accompanied by the offset of the keylights and the onset of the magazine light. All other completions of the four-response chain produced a .5-sec presentation of the grain magazine, which was accompanied by the offset of the keylights. When the pigeon pecked an incorrect key (e.g., the left or right key when the center key was correct), the error was followed by a 5-sec timeout. During the timeout the keys were dark and responses were ineffective. An error did not reset the chain; i.e., the keylights after the timeout were the same color as before the timeout. Each daily session was terminated after 40 food reinforcements. A "blackout" (all lights off) of variable duration preceded and followed each session.

To establish a steady state of repeated acquisition, the four-response chain was changed from session to session. The chains were carefully selected to be equivalent in several ways and their ordering was restricted across sessions (see Thompson, 1973). An example of a typical set of six chains is as follows: LRCR, CLRL, LRLC, RCRL, CLCR, RCLC; the order of the associated colors was always the same: yellow, green, red, white (food on the FR 5 schedule).

As in previous research using repeated-acquisition baselines (e.g., Thompson & Moerschbaecher, 1979, 1980), the data for each session were analyzed in terms of (a) the overall response rate (total responses/min, excluding timeouts) and (b) the overall accuracy or percent errors [(errors/total responses) × 100]. In addition to these measures based on session totals, within-session changes in responding were monitored by an event recorder. For example, acquisition of a response chain was indicated by within-session error reduction, i.e., a decrease in the frequency of errors (per reinforcement) as the session progressed.

Drug testing. Before the drug testing began, the behavior under the baseline schedule was stabilized. The behavior was considered stable when the response rate and percent errors no longer showed systematic change from session to session. After baseline stabilization (30 to 40 sessions), dose-effect data were obtained for *d*-amphetamine. Each of four doses of *d*-amphetamine sulfate (1, 2, 4, and 8 mg/kg) was tested once in a mixed order. The drug was dissolved in saline and injected intramuscularly 30 min presession. Three doses of chlorpromazine hydrochloride (2, 4, and 8 mg/kg) were then tested. The protocol for testing chlorpromazine was the same as that used with *d*-amphetamine, except that there were two determinations for the 4 and 8 mg/kg doses of chlorpromazine. Each of the four doses of *d*-amphetamine (in a mixed order) was then administered in combination with 4 mg/kg of chlorpromazine. Both drugs were injected intramuscularly (one on the right side, the other on the left) 30 min presession. Finally, the dose-effect data for *d*-amphetamine alone were redetermined. Throughout testing,

drug sessions were separated by at least five days, during which time there were baseline sessions and a control session (saline alone injected intramuscularly 30 min presession). The volume of each injection was .1 ml/100 g body weight.

RESULTS

Figure 1 shows the effects of varying doses of *d*-amphetamine and chlorpromazine, administered alone and in combination, on the overall response rate and percent errors for each subject. The brackets at C indicate the control ranges (based on 17 saline sessions). A dose was considered to have an effect on response rate or percent errors to the extent that the data point fell outside of the control range. The points connected are those of the first determination. When *d*-amphetamine was administered alone, the response rate decreased and the percent errors increased with increasing doses. When chlorpromazine was administered alone, there was no effect on response rate or percent errors except at the highest dose. The 8 mg/kg dose of chlorpromazine decreased the response rate and increased the percent errors, though the magnitude of both effects was smaller than with the same dose of *d*-amphetamine. When *d*-amphetamine was administered in combination with 4 mg/kg of chlorpromazine, its rate-decreasing effects were attenuated. At the same time, however, the error-increasing effects of *d*-amphetamine were augmented, except at the highest dose. Note that 1 mg/kg of *d*-amphetamine in combination with chlorpromazine increased the percent errors, whereas there was no effect when this dose of *d*-amphetamine was administered alone.

Figure 2 shows some within-session data from a representative saline session (one that approximated the median for both rate and accuracy) and from several drug sessions for Pigeon 4039. In the event record for each session, the upper and lower pens were deflected downward with each correct response and error, respectively. The data from the first part of each session (the first 10 food reinforcements) are shown; the arrow above each record indicates the fifth reinforcement. As can be seen in the saline record (top), errors de-

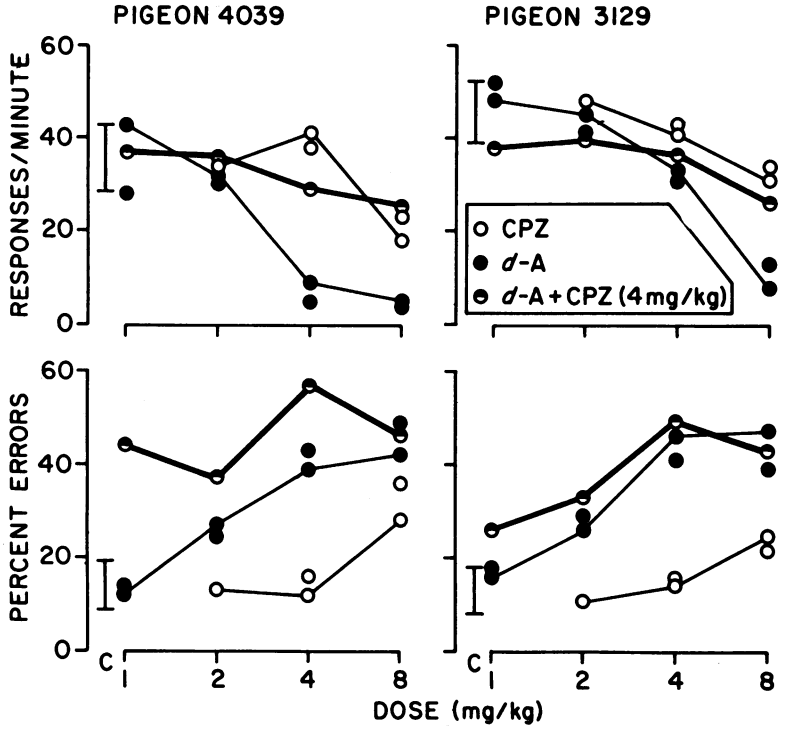

Fig. 1. Effects of varying doses of *d*-amphetamine and chlorpromazine, administered alone and in combination, on the overall response rate and percent errors for each subject. The brackets at C indicate the control ranges (based on 17 saline sessions). The points connected are those of the first determination.

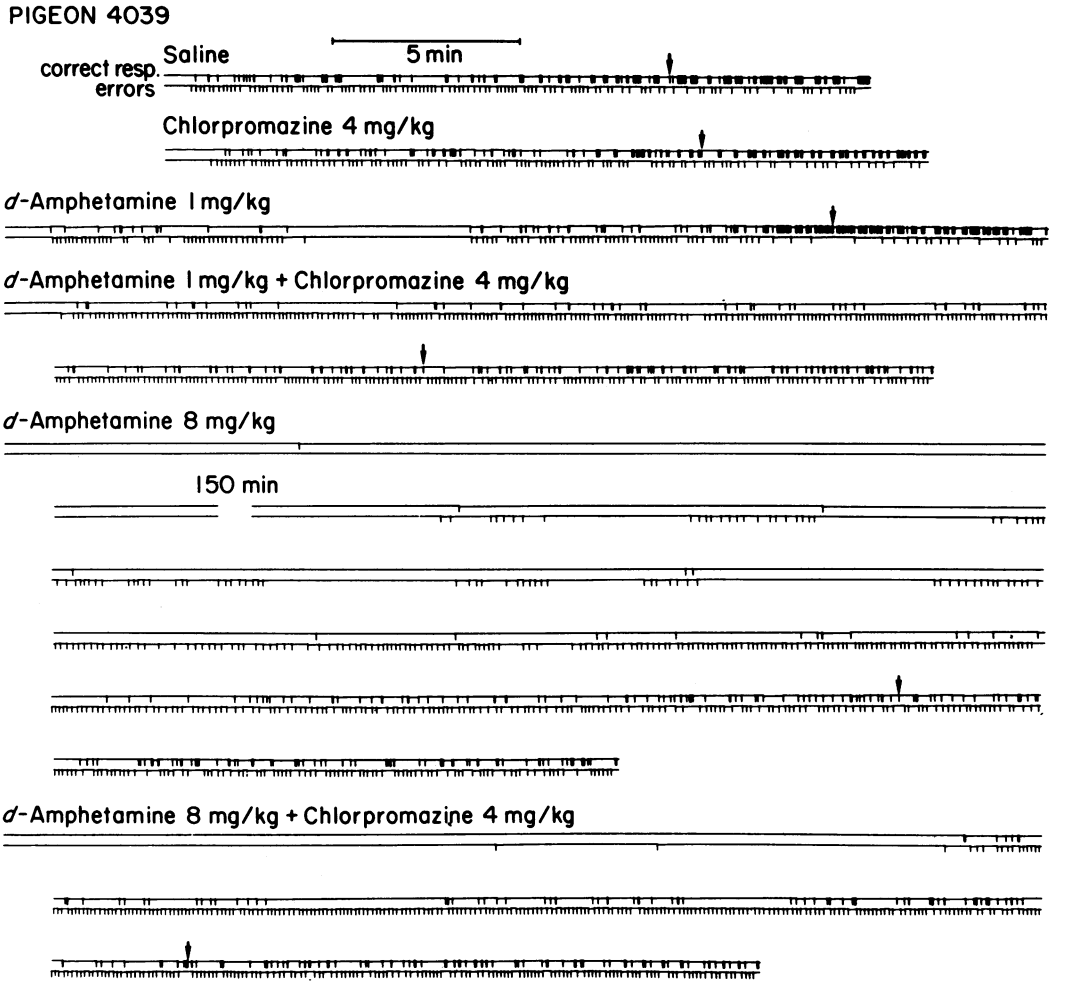

Fig. 2. Within-session data from a representative saline session and from several drug sessions for Pigeon 4039. In the event record for each session, the upper and lower pens were deflected downward with each correct response and error, respectively. The data from the first part of each session (the first 10 food reinforcements) are shown; the arrow above each record indicates the fifth reinforcement. A 150-min period of no responding has been omitted from one record (*d*-Amphetamine 8 mg/kg) at the point indicated.

creased in frequency as the session progressed; i.e., acquisition occurred. After the fifth reinforcement in this session, the correct responses were emitted at a high rate and relatively few errors were made. When 4 mg/kg of chlorpromazine (second determination) was administered alone, the within-session pattern of responding was similar to that in the saline session. When 1 mg/kg of *d*-amphetamine (second determination) was administered alone, some pausing occurred near the beginning of the session, but there was little if any effect on acquisition in terms of error reduction. In contrast, when the same dose of *d*-amphetamine was administered in combination with 4 mg/kg of chlorpromazine, acquisition was clearly disrupted. Errors occurred at a higher frequency than in the saline session and there was less within-session error reduction. When 8 mg/kg of *d*-amphetamine (second determination) was administered alone, there was virtually no responding for a long period of time (a 150-min period of no responding has been omitted from the record at the point indicated). After the extended pausing, errors were relatively frequent; some within-session error reduction did occur, however. When 8 mg/kg of *d*-amphetamine was administered in combination with 4 mg/kg of chlorpromazine, there was considerably less pausing than after this dose of *d*-amphetamine alone, but acquisition was still disrupted. In general, the

within-session drug effects shown in Figure 2 were replicated with the other subject, though the effects (not shown) tended to be smaller.

DISCUSSION

As the dose of *d*-amphetamine alone was increased (first determination), the overall response rate decreased, the overall accuracy was impaired (i.e., percent errors increased), and there was less within-session error reduction (acquisition). These results are consistent with the disruptive effects previously found with *d*-amphetamine in studies where pigeons (Thompson, 1973, 1978; Thompson & Moerschbaecher, 1980) and monkeys (Thompson & Moerschbaecher, 1979) repeatedly acquired four-response chains under an FR 5 schedule. When the dose of *d*-amphetamine was then increased in combination with 4 mg/kg of chlorpromazine, the rate-decreasing effects of *d*-amphetamine were attenuated, but its error-increasing effects were augmented. The shift in the dose-effect curve for rate can not be attributed to the development of behavioral tolerance to *d*-amphetamine since the effects of *d*-amphetamine alone were replicated after the combinations of the two drugs were tested (see the unconnected closed points in Figure 1, top). Probably the most reasonable interpretation of the shifts in the dose-effect curves is that chlorpromazine antagonized the effects of *d*-amphetamine on response rate, but potentiated its disruptive effects on accuracy. The effects obtained when *d*-amphetamine and chlorpromazine were combined could not have been readily predicted on the basis of the effects of these drugs when administered alone (cf. Branch, 1974; Dews, 1976) since 4 mg/kg of chlorpromazine alone was ineffective.

The present finding that chlorpromazine attenuated the effects of *d*-amphetamine on response rate is consistent with previous research. Davis (1965) reported that chlorpromazine antagonized the rate-decreasing effect of *d*-amphetamine in pigeons responding under an FR schedule on a single key. Similar results have been obtained in rats (Brown, 1963) and monkeys (Dalrymple & Stretch, 1971). The generality of these previous findings is therefore extended by the present research, which involved more complex operant behavior.

The present finding that chlorpromazine augmented the disruptive effects of *d*-amphetamine on accuracy complements the results reported by Branch (1974). In that study "pigeons were trained on a procedure where the number of pecks required on a center key (fixed-ratio) signalled which of two side keys was 'correct'" (Branch, 1974, p. 33). It was found that *d*-amphetamine and pentobarbital acted synergistically in decreasing accuracy, even though the two drugs acted antagonistically on response rate (center key). As in the present research, the nature of the joint effect of *d*-amphetamine and another drug depended on the behavioral measure: rate vs. accuracy.

Traditionally, response rates have been treated as implicit to the very definition of operant discrimination. Clearly that assumption bears examining on the basis of the present data. When *d*-amphetamine and chlorpromazine were combined, accuracy was disrupted but there was little or no effect on response rate (Figure 1). In other words, accuracy was a more sensitive indicator of a drug effect on discriminative responding. The selective nature of the *d*-amphetamine–chlorpromazine antagonism also raises a question about the putative neurotransmitter-receptor interactions involved.

REFERENCES

Branch, M. N. Behavior as a stimulus: Joint effects of *d*-amphetamine and pentobarbital. *Journal of Pharmacology and Experimental Therapeutics,* 1974, **189,** 33-41.

Brown, H. *d*-Amphetamine-chlorpromazine antagonism in a food reinforced operant. *Journal of the Experimental Analysis of Behavior,* 1963, **6,** 395-398.

Brown, H. Chlorpromazine-methamphetamine antagonism in a non-discriminated avoidance schedule. *Psychonomic Science,* 1966, **6,** 95-96.

Dalrymple, S. D., & Stretch, R. Effects of amphetamine and chlorpromazine on second-order escape behavior in squirrel monkeys. *Psychopharmacologia,* 1971, **21,** 268-282.

Davis, J. L. Antagonism of a behavioral effect of *d*-amphetamine by chlorpromazine in the pigeon. *Journal of the Experimental Analysis of Behavior,* 1965, **8,** 325-327.

Dews, P. B. Interactions of behavioral effects of drugs. *Annals of the New York Academy of Sciences,* 1976, **281,** 50-63.

Iversen, S. D., & Iversen, L. L. *Behavioral pharmacology.* New York: Oxford University Press, 1975.

Ray, O. S., & Bivens, L. W. Anticholinergic potentiation of amphetamine: Reinforcement schedule effects. *Archives Internationales de Pharmacodynamie et de Therapie,* 1968, **172,** 414-420.

Teitelbaum, P., & Derks, P. The effect of amphetamine on forced drinking in the rat. *Journal of*

Comparative and Physiological Psychology, 1958, **51,** 801-810.

Thompson, D. M. Repeated acquisition as a behavioral baseline for studying drug effects. *Journal of Pharmacology and Experimental Therapeutics,* 1973, **184,** 506-514.

Thompson, D. M. Stimulus control and drug effects. In D. Blackman & D. Sanger (Eds.), *Contemporary research in behavioral pharmacology.* New York: Plenum, 1978.

Thompson, D. M., & Moerschbaecher, J. M. An experimental analysis of the effects of *d*-amphetamine and cocaine on the acquisition and performance of response chains in monkeys. *Journal of the Experimental Analysis of Behavior,* 1979, **32,** 433-444.

Thompson, D. M., & Moerschbaecher, J. M. Effects of *d*-amphetamine and cocaine on strained ratio behavior in a repeated-acquisition task. *Journal of the Experimental Analysis of Behavior,* 1980, **33,** 141-148.

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